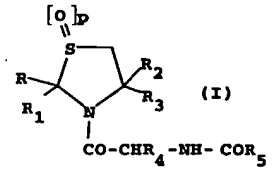
94-242602/30 B03 RHON.93.01.07
RHONE POULENC RORER SA *FR 2700168-A1
93.01.07 93FR-000076 (94.07.08) C07D 277/04, A61K 31/425, C07D 277/10

New thiazolidine derivs. with affinity for cholecystokinin and gastrin receptors - are used to treat e.g. psychosis, anxiety, irritable colon syndrome, tumours and pancreatitis.

C94-110770

Addnl. Data: DUBROEUCQ M, MANFRE F

Thiazolidine derivs. of formula (I) and their salts and isomers are new:



B(7-F1, 14-J2C) .2

R = 1-12C alkyl, 3-12C cycloalkyl or 6-12C polycycloalkyl (all opt. mono or polyunsatd); phenylalkyl, (opt. ring-substd. by alkyl, alkoxy and/or halo); diphenylalkyl; cinnamyl; pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd. by one or more alkyl); or phenyl (opt. substd. by halo, alkyl, alkoxy, OH, NO_2, amino, mono- or di-alkylamino, alkoxycarbonyl, $CONR_7R_8$, NHCOMe, CF_3, Ph and/or OCF_3); oxo-2-piperidyl; or quinuclidinyl;
R_1, R_3 = H , alkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl and/or alkoxy);
R_2 = $(CH_2)_n$- COR_6, $(CH_2)_mOCOR''_6$, -$(CH_2)_mNR_9R_{10}$ or oxazolinyl (opt. substd. by alkyl, and/or alkyl-3-oxadiazolyl);
R_4 = H or alkyl;
R_5 = phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio), naphthyl, indolyl, quinolyl, or phenylamino (opt. ring substd. by halo, alkyl, alkoxy, alkylthio, CF_3, COOH, alkoxycarbonyl, OH, NO_2, amino, acyl, CN, sulphamoyl, carbamoyl, hydroxyimino alkyl, alkoxyiminoalkyl, hydroxyamino carbonyl,

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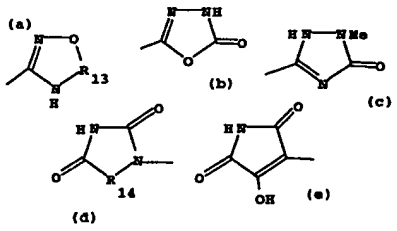
alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphinyl, mono- or polyhydroxyalkyl, sulpho, alk-O-CO-alk, alk-COOX, alk-O-alk, alk^1-COOX, O-alk-COOX, CH=CHCOOX, $COCO_2X$, $alkSO_3H$ (or its salt), CH=CH-alk^1, C(=NOH)CO_2X, S-alk-CO_2X, SO-alk-CO_2X, SO_2-alk-CO_2X, OCH_2alk^1-COOX, CX=N-O-alk-CO_2X, alk-N(OH)-CO-alk, $alkSO_2H$, SO_2NHCOR_{11}, $SO_2NHSO_2R_{11}$, $CONHCOR_{11}$, $CONHSO_2R_{11}$, $B(OH)_2$, $C(NH_2)$=NOH, SO_2NHR_{12}, $CONHR_{12}$, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl or a gp. of formula (a)-(e);



R_6 = OH, alkoxy, cycloalkoxy, cycloalkyl-alkoxy, phenyl or NR_9R_{10};
R''_6 = alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl or NR_9R_{10};
R_7 = H, alkyl, phenyl alkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio);
R_8 = alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio);
or NR_7R_8 = mono- or polycyclic opt. unsatd. heterocycle contg. 4-9C atoms and 1 or more O or N atoms and opt substd. by one or more alkyl;
R_9 = H, alkyl, cycloalkylalkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio),
R_{10} = alkyl, cycloalkyl, cycloalkylalkyl; phenylalkyl, or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio);
or NR_9R_{10} = mono- or polycyclic opt. unsatd. heterocycle contg. 4-9C and 1 or more O,N and S, and opt. substd. by one or more alkyl;
R_{11} = alkyl, cycloalkyl, CF_3 or phenyl (opt. substd by CN, alkoxy, NO_2, amino and/or halo);
R_{12} = tetrazol-5-yl;
R_{13} = CO or SO;
R_{14} = O or CO;
n, p = 0-2;

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m = 1 or 2;
X = H, alkyl, or phenyl alkyl;
alk = alkyl or alkylene; and
alk^1 = hydroxyalkyl, hydroxyalkylene, alkoxyalkyl or alkoxyalkylene;
unless otherwise stated all alkyl moieties contain 1-4C; acyl moieties contain 2-4C and cycloalkyl moieties contain 3-6C;
provided that : n is not 0 when R, R_3 = H and R_1 = pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd by one or more alkyl) or phenyl (opt. substd by halo, alkyl, alkoxy, OH, NO_2, amino, mono- or di-alkylamino, alkoxycarbonyl, $CONR_7R_8$, NHCOMe, CF_3 or OCF_3).

USE

(I) have strong affinity for cholecystokinin (CCK) and gastrin receptors. They are particularly useful in the treatment and prevention of disorders due to CCK and gastrin in the nervous system and GI tract. They are used to treat and prevent psychoses, anxiety, depression, neurodegeneration, panic attacks, Parkinson's disease, tardive dyskinesia, irritable bowel syndrome, pancreatitis, ulcers, intestinal motility disorders, certain tumours sensitive to CCK, memory dysfunction, chronic withdrawal and abuse of alcohol or drugs, as pupil constrictors, analgesics or as potentiators for analgesics (both narcotic and non narcotic), and as appetite regulators.

DOSAGE

Dosage is pref. oral at 0.05-1g/day in unit doses of 10-500 mg.

ADVANTAGE

(I) have low toxicity e.g. LD_{50} of more than 40 mg/kg in mice.

PREPARATION

4 methods are claimed e.g. as follows: (I; p = 0, R_5=R_5') is prepd. by reacting a carbamic acid deriv. obtd. opt. in situ by reaction of a carbonic acid deriv. chosen from N,N^1-diimidazolecarbonyl, phosgene, triphosgene and p-nitrophenyl-chloroformate with a thiazo cpd. of formula (II), and with an aniline deriv. where the phenyl ring is opt. substd. by Q, and opt. salifying.

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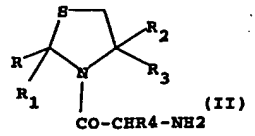

(II)

R_5^1 = phenylamino (opt. ring substd.);
Q = halo, alkyl, alkoxy, alkylthio, CF_3, COOH, alkoxycarbonyl, OH, NO_2, amino, acyl, CN, sulphamoyl, carbamoyl, hydroxyiminoalkyl, alkoxyiminoalkyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphinyl, mono- or polyhydroxyalkyl, sulpho, alk OCOalk, alkCOOX, alkO-alk, alk^1-COOX, O-alkCOOX, CH=CHXCOOX, $COCO_2X$, $alkSO_3H$, $CH=CH-alk^1$, $C(=NOH)-CO_2X$, S-$alkCO_2X$, $SOalkCO_2X$, SO_2alkCO_2X, $OCH_2alk^1CO_2X$, CX=NO-alk-CO_2X, alk-N(OH)-CO-alk, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl, $alkSO_2H$, SO_2NHCOR_{11}, $SO_2NHSO_2R_{11}$, $CONHCOR_{11}$, $CONHSO_2R_{11}$, $B(OH)_2$, $C(NH_2)=NOH$, SO_2NHR_{12}, $CONHR_{12}$ or a gp. (a)-(e).

Cpds. (I) may be interconverted.

EXAMPLE

A soln. of 1.38g (4R)- tertbutyl 3-(2-aminoacetyl) 2-cyclohexyl 4-thiazolidine carboxylate in 25ml $CHCl_3$ was treated at 25°C with 1.1g benzyl 3-isocyanatophenylacetate in 10ml $CHCl_3$. The mixt was stirred for 12hrs at 25°C, conc., and worked up to give 2.1g benzyl (4R)- 3-(3-(2-(4-tertbutoxy carbonyl-2-cyclohexyl 3-thiazolidinyl) 2-oxo-ethyl) ureido) phenylacetate. 2g this prod.,1.7g ammonium formate and 2g 10% Pd/C were treated with 30cm^3MeOH slowly under inert atmos. The mixt was refluxed for 2hrs and cooled to 25°C. The catalyst was filtered off and the filtrate was conc. and dried under reduced pressure at 40°C. The residue was dissolved in 25cm^3 aq 1N NaOH, and washed with Et_2O (2x10ml). The aq phase was adjusted to pH2 by addn of aq. 1N H_2SO_4. The ppte was filtered, washed and air dried to give 1g of (4R)-3(3(2-4-tertbutoxy carbonyl 2-cyclohexyl 3-thiazolidinyl) 2-oxoethyl-ureido) phenylacetic acid

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m.pt. 115°C.

In tests (I) have IC_{50} value of < 1000nM for inhibition of binding to CCK receptors. (59pp1858DwgNo.0/0)